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Design and synthesis of novel, conformationally restricted HMG-CoA reductase inhibitors

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Abstract—Using structure-based design, a novel series of conformationally restricted, pyrrole-based inhibitors of HMG-CoA reductase were discovered. Leading analogs demonstrated potent inhibition of cholesterol synthesis in both in vitro and in vivo models and may be useful for the treatment of hypercholesterolemia and related lipid disorders.

Despite advances in diagnosis and treatment, coronary heart disease (CHD) remains a leading cause of death worldwide.[1] HMG-CoA reductase inhibitors, which block the rate limiting step of cholesterol synthesis, represent the current standard of care for patients with risk factors for CHD.[2,3] As a class, these drugs are well tolerated and remarkably effective. However, as new revisions to National Cholesterol Education Program (NCEP) cholesterol treatment guidelines call for increasingly aggressive LDL-C lowering in at-risk patients (for example, LDL-C < 70 mg/dl for highest risk patients)[4] there is continued need for novel HMG-CoA reductase inhibitors with increased efficacies.

As described in the preceding paper, during a program to discover new HMG-CoA reductase inhibitors, we identified a series of substituted *N-iso*-propyl pyrroles (**2**, Fig. 1) which represent a regioisomeric variation of the atorvastatin (**1**) template and offer a unique pharmacological profile and excellent potency against HMG-CoA reductase (**2**: IC_{50} = 1.8 nM).[5] Structural biology studies with inhibitor **2** (Fig. 2) revealed that it bound to the active site of HMG-CoA reductase consistent with the binding mode of other known statins.[6,7] Interestingly, examination of the bound conformation of **2** revealed the close proximity (1.9 Å) of the amide NH–hydrogen and the *ortho*-hydrogen of the adjacent phenyl A-ring (see Fig. 2). This proximity suggested the opportunity for constructing conformationally restricted analogs of general structure **3** (Fig. 3).[8] It is precedented that reducing the number of rotatable bonds in a ligand can, under appropriate circumstances, lead to an increase in the free energy of binding due to a reduction

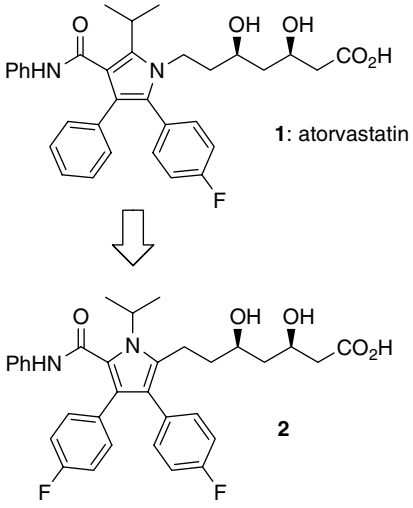

Figure 1. Structure of HMG-CoA reductase inhibitors **1** and **2**.

Keywords: HMG-CoA reductase inhibitor; Statin; Hypercholesterolemia.
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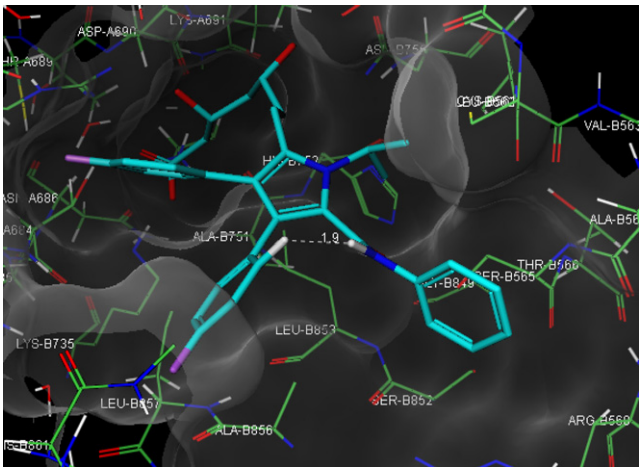


Figure 2. X-ray crystal structure (2.1 Å resolution) of inhibitor **2** bound to the active site of HMG-CoA reductase illustrating the potential for introduction of a conformational restriction.

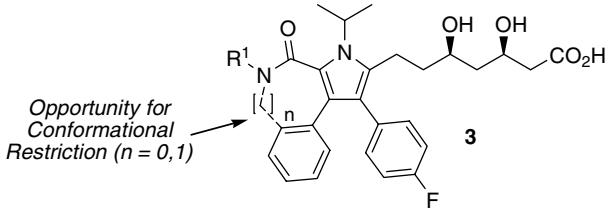
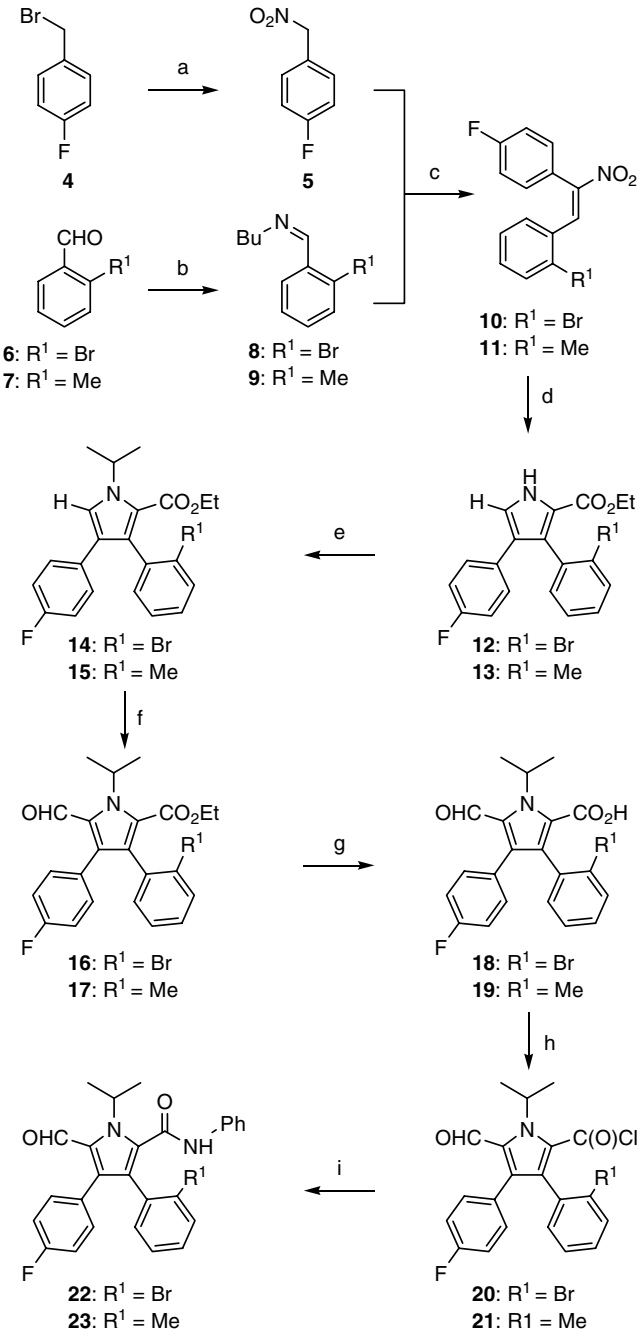


Figure 3. General structure of conformationally restricted HMG-CoA reductase inhibitors.

in the entropic cost of binding.[9] Moreover, the success of such strategies is typically enhanced when the bound conformation of the ligand is established. To determine if such a conformation restriction would be beneficial in the current series, a set of prototype analogs were prepared and evaluated as described herein.

Synthesis of prototype inhibitors. Compounds for the current studies were prepared as outlined in Schemes 1–4. As illustrated in Scheme 1, a Barton–Zard synthesis[10] was employed to construct key pyrrole intermediates **22** and **23**.[11] Initially, 4-fluorobenzyl bromide (**4**) was reacted with $AgNO_2$ to provide compound **5**. In parallel, 2-bromobenzaldehyde (**6**) was condensed with *n*-butylamine to generate imine **8**. Reaction of **5** and **8** in AcOH at ambient temperature provided nitroalkene **10**. Subsequent reaction of nitroalkene **10** with ethyl isocyanoacetate in the presence of DBU resulted in formation of pyrrole **12**. N-Alkylation of pyrrole **12** was accomplished with *i*-propyl iodide and KOH to give **14** which was formylated under Vilsmeier–Haack conditions to afford pyrrole carboxaldehyde **16**. Saponification of **16** followed by conversion to the corresponding acid chloride and reaction with aniline gave anilide **22** as a key intermediate for subsequent analog synthesis. Separately, intermediate **23** was prepared from *o*-tolualdehyde (**7**) via a similar protocol.

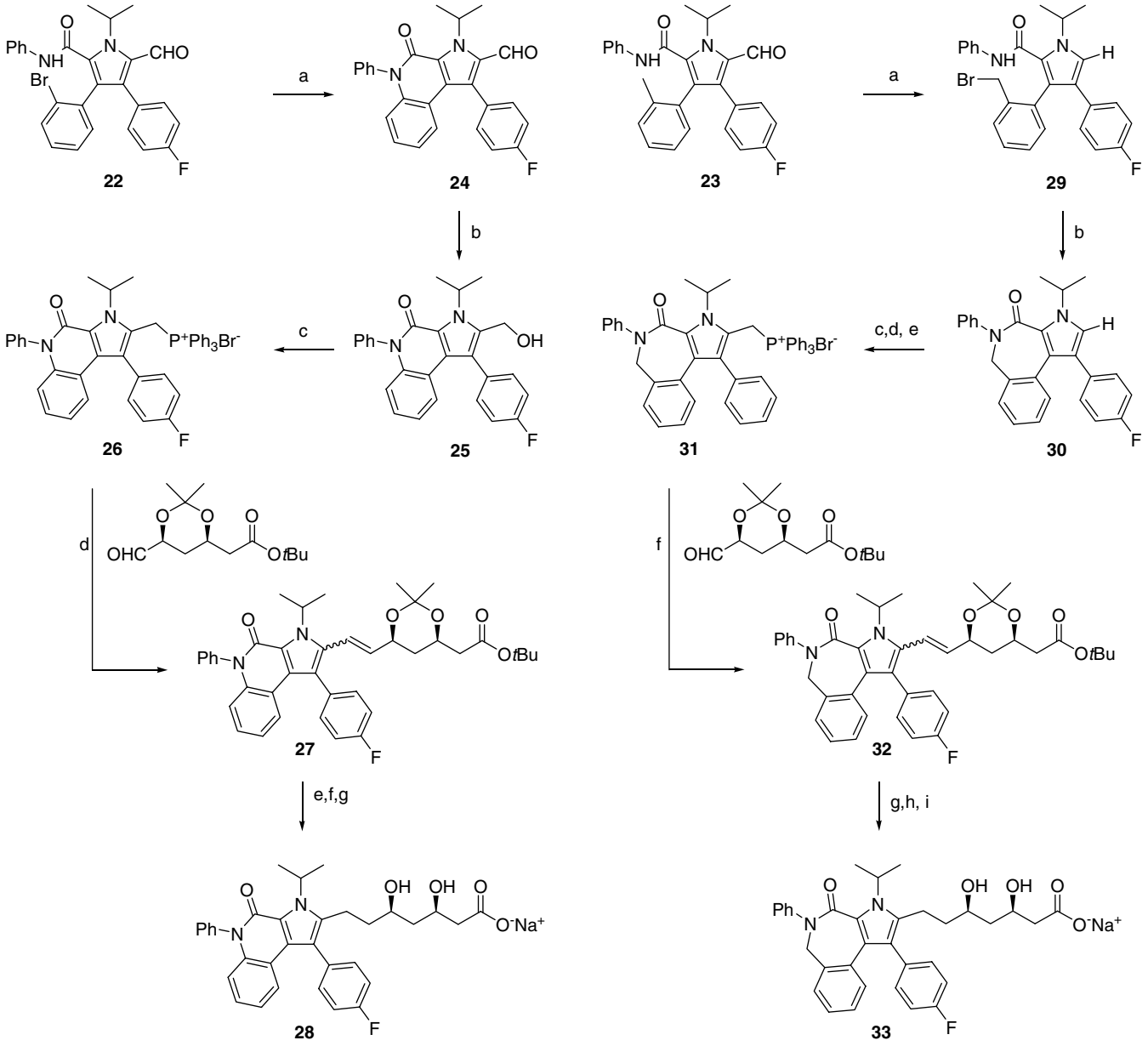
With pyrrole **22** in hand, analogs such as **28** which contained a 6-membered fused ring system were prepared as outlined in Scheme 2. Initially, **22** was treated with



Scheme 1. Reagents and conditions: (a) $AgNO_2$, Et_2O, 0 → 25 °C, 24 h, 68%; (b) *n*-$BuNH_2$, toluene, 120 °C, 2 h, 99%; (c) AcOH, 25 °C, 14 h, 78–92%; (d) DBU, ethyl isocyanoacetate, THF, 25 °C, 8 h, 33%; (e) KOH, *i*-PrI, DMSO, 25 °C, 2 h, 51–61%; (f) $POCl_3$, DMF, dichloroethane, 80 °C, 18 h, 59–84%; (g) NaOH, MeOH, 60 °C, 3 h, 83–85%; (h) $SOCl_2$, 70 °C, 1 h; (i) $PhNH_2$, Et_3N, CH_2Cl_2, 0 → 25 °C, 12 h, 18–51% (two steps).

$Pd(OAc)_2$, (9,9-dimethyl-4,5-bis(diphenylphosphino))-xanthane, and Cs_2CO_3 at elevated temperature to affect a Buchwald aryl-amidation reaction that generated lactam **24**.[12]

Installation of the 3,5-dihydroxyhexanoic acid side-chain began with reduction of the pyrrole carboxaldehyde **24** to the corresponding alcohol **25**. Treatment of

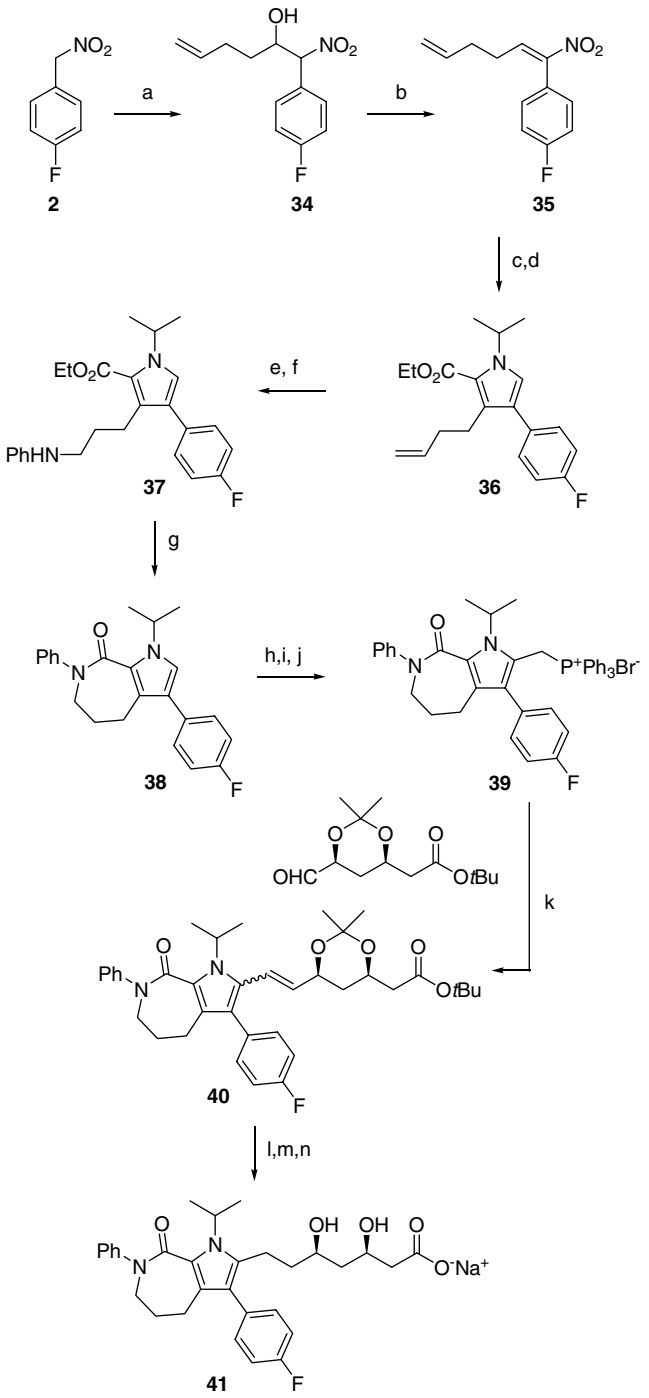


Scheme 2. Reagents and conditions: (a) $Pd(OAc)_2$, ((9,9-dimethyl-4,5-bis(diphenylphosphino))xanthane, Cs_2CO_3, toluene, 100 °C, 16 h, 37%; (b) $LiAl(O\text{-}t\text{-}Bu)_3H$, THF, 0 °C, 0.5 h, 49%; (c) $Ph_3P{\cdot}HBr$, CH_2Cl_2, 50 °C, 2 h, 100%; (d) *n*-BuLi, THF, −78 → 25 °C, 2 h, 54%; (e) HCl, MeOH, 25 °C, 12 h, 81%; (f) Pd–C, H_2, EtOH, 25 °C, 6 h, 74%; (g) NaOH, MeOH, 25 °C, 8 h, 95%.

Scheme 3. Reagents and conditions: (a) AIBN, NBS, CCl_4, 80 °C, 2 h, 15%; (b) NaH, THF, 0 → 25 °C, 3 h, 84%; (c) $POCl_3$, DMF, dichloroethane, 80 °C, 18 h, 80%; (d) $LiAl(O\text{-}t\text{-}Bu)_3H$, THF, 0 °C, 0.5 h, 67%; (e) $Ph_3P{\cdot}HBr$, CH_2Cl_2, 50 °C, 2 h, 100%; (f) *n*-BuLi, THF, −78 → 25 °C, 2 h, 65%; (g) HCl, MeOH, 25 °C, 12 h; (h) Pd–C, H_2, EtOH, 25 °C, 6 h, 69% (two steps); (i) NaOH, MeOH, 25 °C, 8 h, 54%.

25 with $Ph_3P{\cdot}HBr$ resulted in quantitative conversion to phosphonium salt **26**.[13] Deprotonation of **26** with *n*-BuLi afforded a ylide that was reacted with *t*-butyl-2-((4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate[14] to provide olefin **27** as an inconsequential mixture of geometric isomers. The acetonide protecting group of **27** was removed by treatment with HCl/MeOH, the side-chain olefin was hydrogenated over 10% Pd/C, and the terminal ester was saponified with aqueous NaOH to provide **28** as its carboxylate sodium salt.

Analogs such as **33** which contained a 7-membered fused ring were prepared from pyrrole intermediate **23** as outlined in Scheme 3. First, radical bromination of the ortho-methyl position with NBS/AIBN provided benzyl bromide **29**. Unexpectedly, this radical reaction resulted in concomitant deformylation of the pyrrole ring. Various attempts to suppress this deformylation reaction were unsuccessful; consequently, intermediate **29** was progressed forward in the synthesis. To effect a nucleophilic ring closing reaction, **29** was treated with NaH to provide compound **30** in good yield. Vilsmeier–Haack formylation of **30** then re-installed the carboxaldehyde motif which was subsequently reduced to the corresponding alcohol with $LiAl(O\text{-}t\text{-}Bu)_3H$. This alcohol was then treated with $Ph_3P{\cdot}HBr$ to afford phosphonium salt **31**. Deprotonation of **31** with *n*-BuLi



Scheme 4. Reagents and conditions: (a) $CH_2{=}CH(CH_2)_2CHO$, KF, *i*-PrOH, 25 °C, 16 h, 59%; (b) trifluoroacetic anhydride, Et_3N, CH_2Cl_2, −10 °C, 0.5 h, 84%; (c) DBU, ethyl isocyanoacetate, THF, 25 °C, 18 h, 92%; (d) KOH, *i*-PrI, DMSO, 25 °C, 2 h, 75%; (e) $NaIO_4$, OsO_4 (cat.) THF:H_2O, 0 → 25 °C, 18 h, 52%; (f) $PhNH_2$, $Na(OAc)_3BH$, AcOH, dichloroethane, 25 °C, 18 h, 79%; (g) Me_3Al, Et_3N, CH_2Cl_2:toluene, 60 °C, 16 h, 94%; (h) $POCl_3$, DMF (cat.) dichloroethane, 80 °C, 18 h, 97%; (i) $LiAl(O\text{-}t\text{-}Bu)_3H$, THF, 0 °C, 0.5 h, 56%; (j) $Ph_3P{\cdot}HBr$, CH_2Cl_2, 50 °C, 2 h, 100%; (k) NHMDS, THF, −78 → 25 °C, 1 h, 85%; (l) HCl, MeOH, 25 °C, 2 h, 84%; (m) 10% Pd–C, H_2, MeOH, 25 °C, 6 h, 72%; (n) NaOH, MeOH, 25 °C, 4 h, 96%.

followed by addition of *t*-butyl 2-((4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate[14] resulted in the formation of olefin **32** as a mixture of geometric isomers. Intermediate **32** was then subjected to the same deprotection, hydrogenation, and saponification sequence described above to provide compound **33** as its carboxylate sodium salt.

A third type of analog, bearing a 7-membered ring fusion but lacking the phenyl A-ring, was prepared as outlined in Scheme 4. Henry reaction between compound **2** and 4-pentenal afforded β-nitro alcohol **34** that, in a separate step, underwent elimination upon treatment with trifluoroacetic anhydride and triethylamine to nitro alkene **35**.[15,16] Reaction of **35** with ethyl isocyanoacetate in the presence of DBU resulted in formation of a pyrrole which was subsequently alkylated with *i*-propyl iodide to provide **36**. The terminal olefin of **36** was oxidatively cleaved to an intermediate aldehyde that was subjected to reductive amination conditions [$PhNH_2$, $Na(OAc)_3H$] to afford secondary amine **37**. Treatment of amine **37** with trimethyl aluminum at elevated temperature effected efficient conversion to lactam **38**.[17] Vilsmeier–Haack formylation, reduction, and reaction with Ph_3PHBr converted **38** into triphenyl phosphonium salt **39** which was then engaged in a Wittig olefination reaction with *t*-butyl 2-((4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate[14] to produce olefin **40** as a *cis*/*trans* mixture. Intermediate **40** was then subjected to the same deprotection, hydrogenation, and saponification sequence described above to provide compound **41** as its carboxylate sodium salt.

The methods outlined in Schemes 1–4 were subsequently utilized to prepare a series of analogs as highlighted in Tables 1 and 2.

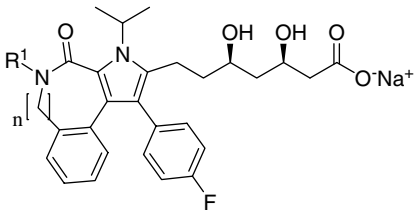
Structure–activity studies. All new analogs were initially evaluated in a microsomal HMG-CoA reductase assay.[18] Analogs were also evaluated for their ability to inhibit cholesterol synthesis in primary rat hepatocyte cells.[18] Additionally, compounds with promising in vitro activities were then evaluated in an acute in vivo efficacy model.[18]

As shown in Table 1, several SAR trends were noted. First, comparison of reference compound **2** (IC_{50} = 1.8 nM) to its 6- and 7-membered conformationally constrained counterparts **28** (IC_{50} = 16.7 nM) and **33** (IC_{50} = 9.6 nM), respectively, revealed that introduction of the conformational restriction resulted in a 5- to 10-fold loss in enzyme inhibition potency. There was little difference in enzyme potency between the 6- and 7-membered conformational restrictions (i.e., **28** vs **33**).

Unexpectedly, whereas reference compound **2** was equipotent in the enzyme (IC_{50} = 1.8 nM) and cellular assays (IC_{50} = 1.0 nM) both conformationally constrained prototype compounds (**28** and **33**) were substantially less active (10- to 100-fold) in the hepatocyte cellular assay relative to the enzyme assay as illustrated by the data in Table 1.

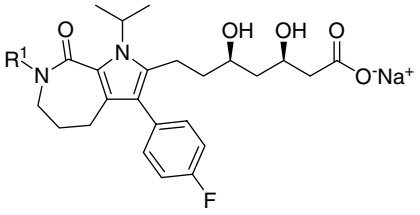
To better understand the SAR of this conformationally constrained series, a selected set of substituted anilides (**42**–**44**), benzyl amides (**45**–**48**), and a secondary amide

Table 1. Inhibitory activity of analogs **28**, **33**, and **42** – **49** against HMG-CoA reductase and hepatocyte cholesterol synthesis[18]



	R^1	n	HMG-CoA IC_{50} (nM)	Hepatocyte inhibition CS IC_{50} (nM)	Preparation method (scheme)
Simvastatin	—	—	49	4.0	—
2	—	—	1.8	1.0	—
28	Ph	0	16.7	1250	2
33	Ph	1	9.6	94	3
42	3-F Ph	0	1.9	246	2
43	3-Cl Ph	0	2.9	100	2
44	4-F Ph	0	16.4	NT	2
45	Bn	0	13.9	400	2
46	2-F Bn	0	3.0	68	2
47	3-F Bn	0	37.4	NT	2
48	4-F Bn	0	4.7	1000	2
49	H	0	11.7	8.8	2

Table 2. Inhibitory activity of analogs **41** and **50** against HMG-CoA reductase and hepatocyte cholesterol synthesis[18]



	R^1	HMG-CoA IC_{50} (nM)	Hepatocyte inhibition CS IC_{50} (nM)	Preparation method (scheme)
41	Ph	0.3	5.9	4
50	Bn	3.5	0.8	4

(**49**) were synthesized and evaluated as illustrated in Table 1. Notably, installation of a 3-F (**42**) or 3-Cl (**43**) substituent on the anilide ring afforded improved activity against HMG-CoA reductase relative to the unsubstituted case (i.e., **28**). In the benzyl amide series, installation of a 2-F (**46**) or a 4-F (**48**) substituent afforded the best activity. However, in both the anilide analogs (**42**–**44**) and benzyl amide analogs (**45**–**48**) the substantial disconnect between enzyme inhibitory potency and cellular activity persisted. By contrast, secondary amide **49**, where R^1 = H, was equipotent in both enzyme (IC_{50} = 11.7 nM) and cellular assays (IC_{50} = 8.8 nM).

Analogs (**41** and **50**, Table 2) which contained a 7-membered fused ring but lacked the phenyl A-ring were also evaluated. Interestingly both **41** (R_1 = Ph) and **50** (R_2 = Bn) exhibited good potency against HMG-CoA, and they maintained comparable activity in the cellular hepatocyte assay.

As described above, compounds **41**, **49**, and **50** exhibited the best correlation between enzyme and cellular activity whereas the other analogs were substantially less active in cellular assay.[19] Notably, these three analogs each lacked one phenyl ring relative to the other analogs. As a result they had reduced molecular weight and lipophilicity as illustrated by a comparison of **49** (M_W = 480, *c* Log *D* (pH 7.4) = −0.50, HMG-CoA IC_{50} = 11.7 nM, hepatocyte IC_{50} = 8.8 nM) versus **28** (M_W = 556, *c* Log *D* (pH 7.4) = 1.00, HMG-CoA IC_{50} = 16.7 nM, hepatocyte IC_{50} = 1250 nM). One possible explanation for the observed differences in cellular activities is the active transport of selected inhibitors into hepatocyte cells. For example, other known HMG-CoA reductase inhibitors have been reported to undergo active transport into hepatocyte cells via the Organic Anion Transporting Peptide (OATP) family of transporters.[20] It is conceivable that smaller, less lipophilic molecules such as **49** might be better substrates for transport as compared to larger, more lipophilic, more rigid analogs such as **28** thus accounting for the improved cellular activity of the former versus the latter compound.

In order to further characterize the potential of this series of inhibitors, several representative analogs were evaluated in an in vivo efficacy model to measure their ability to acutely inhibit cholesterol synthesis.[18] In this

model, mice were initially dosed with drug (1 mg/kg) and then, after 0.5 h, given an intraperitoneal injection of ^{14}C sodium acetate. After 4.5 h, a whole blood sample was obtained and analyzed for ^{14}C cholesterol levels which were compared to untreated control animals to determine percent inhibition of acute cholesterol synthesis. As illustrated in Table 3, reference compound simvastatin (−45% @ 1 mg/kg) and benchmark compound **2** (−57% @ 1 mg/kg) exhibited robust acute inhibition of cholesterol synthesis in this model. Three representative conformationally constrained analogs (**28**, **41**, and **45**) were then evaluated. Among these compounds, **41** was the most active however, its efficacy was unfortunately inferior to that of the reference compound **2** and simvastatin.

Structural biology. Finally, to better evaluate whether our original hypothesis (that one could lock these inhibitors into their active conformation through a ring fusion) was accurate, we undertook structural biology studies on a representative analog. Figure 4 illustrates an overlay of the crystal structures of compounds **2** and **41** bound independently to the active site of HMG-CoA reductase.[21] As shown, the 7-membered fused ring of **41** allows the amide motif to reasonably approximate the amide conformation of compound **2** thereby maintaining a key hydrogen bond to Ser-565. Minor distortion of the anilide ring was noted. Figure 5 illustrates an overlay of the crystal structures of compounds **2** and **28** bound independently to the active site of HMG-CoA reductase.[21] As expected and in contrast to the case described above, the 6-membered fused ring of inhibitor **28** substantially distorts the amide trajectory compromising the hydrogen bond to Ser-565. Additionally the anilide and phenyl A-rings also experience some distortion. Such changes likely contribute to the reduced potency of **28** (IC_{50} = 16.7 nM) relative to **41** (IC_{50} = 0.3 nM) or **2** (IC_{50} = 1.8 nM).

Table 3. Activity of representative analogs in acute in vivo efficacy model[18]

	HMG-CoA IC_{50} (nM)	Hepatocyte Inhibition CS IC_{50} (nM)	Mouse acute inhibition CS (1 mg/kg) (%)
Simvastatin	49	4.0	−45
2	1.8	1.0	−57
28	16.7	1250	−33
45	13.9	400	−14
41	0.3	5.9	−39

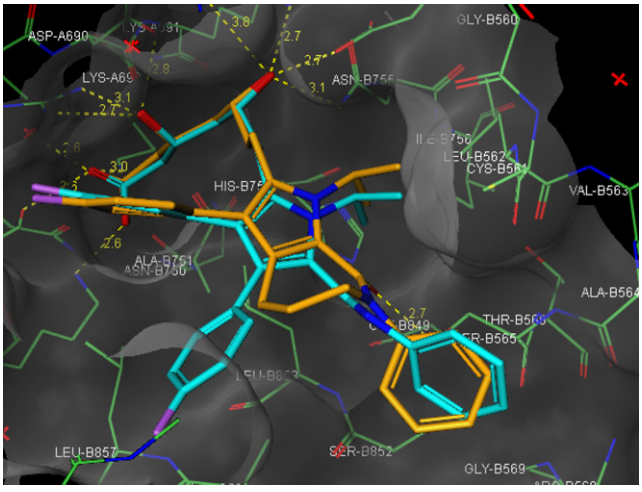


Figure 4. Overlay of X-ray crystal structures of inhibitors **2** [blue] (2.1 Å resolution) and **41** [orange] (2.0 Å resolution) bound to the active site of HMG-CoA reductase.

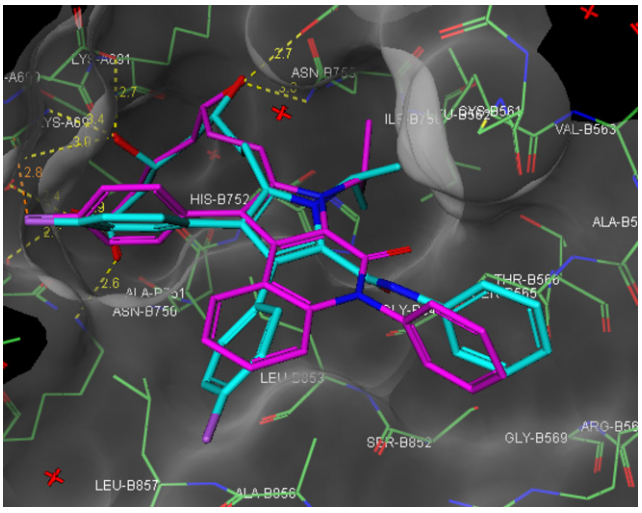


Figure 5. Overlay of X-ray crystal structures of inhibitors **2** [blue] (2.1 Å resolution) and **28** [purple] (2.0 Å resolution) bound to the active site of HMG-CoA reductase.

In conclusion, we have described the structure-based design, synthesis, and biological evaluation of a series of conformational constrained HMG-CoA reductase inhibitors. Selected compounds exhibited good in vitro potencies and demonstrated inhibition of cholesterol synthesis in an acute efficacy model; however, in general these conformationally restricted analogs were less efficacious than their unconstrained counterparts.

Acknowledgments

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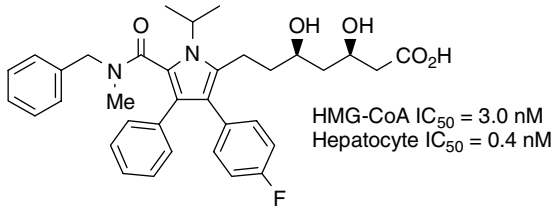
7. Crystallization protocol and PDB coordinates for the X-ray structure in Figure 2 can be found in Ref. 5.
8. Additional evidence that such a conformational restriction might be successful was provided by the fact that the following *N*-methyl benzyl amide analog of compound **2** also demonstrated good potency against HMG-CoA reductase suggesting that N-alkylation necessary for installation of the conformational restriction would be tolerated:



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18. In vitro IC_{50} values are reported as arithmetic mean for $n \geqslant 2$ independent measurements unless otherwise noted. For detailed assay protocols, see: Bratton, L. D.; Auerbach, B.; Choi, C.; Dillon, L.; Hanselman, J. C.; Larsen, S. D.; Lu, G.; Olsen, K.; Pfefferkorn, J. A.; Robertson, A.; Sekerke, C.; Trivedi, B. K.; Unangst, P. C. *Bioorg. Med. Chem.* **2007**, in press. doi:10.1016/j.bmc.2007.05.031.
19. As described in Ref. 5, in addition to in vitro potency and in vivo efficacy, an additional area of interest for HMG-CoA reductase inhibitors is selectivity for hepatocyte cells versus other cell types as this is thought to confer reduced risk of statin-induced mylagia. Given that analogs **41**, **49**, and **50** exhibited good hepatocyte activity, we also evaluated them for selectivity in a myocyte cell line (Ref. 5). Unfortunately, none of these compounds exhibited hepatoselectivity.
20. Hsiang, B.; Zhu, Y.; Wang, Z.; Wu, Y.; Sasseville, V.; Yang, W.-P.; Kirchgessner, T. G. *J. Biol. Chem.* **1999**, *274*, 37161.
21. Coordinates for the X-ray structures in Figures 4 and 5 have been deposited at the PDB under filenames 2Q6B and 2Q6C, respectively.